REMARKS

The Present Invention

The present invention pertains to a lymphocyte having dual specificity, compositions comprising the same, a pharmaceutical composition comprising the same, and a method of preparing the same.

The Pending Claims

Claims 1, 4, 7, 8, 10, 11, 40, 41, 44-61, and 71 are pending. Claims 1, 4, 7, 8, 10, and 46 are directed to a composition comprising a dual specificity T lymphocyte. Claims 11 and 47-51 are directed to a dual specificity lymphocyte. Claims 40 and 52-56 are directed to a pharmaceutical composition comprising a dual specificity T lymphocyte. Claims 41 and 58-61 are directed to a method of preparing lymphocytes having dual specificity, while claim 71 is directed to the lymphocytes made therefrom.

The Office Action

The Office alleges that claims 62-70 are drawn to a non-elected invention, and has withdrawn these claims from consideration. The Office also states that the status of U.S. Application No. 08/547,263 (the '263 application), which is cited on page 17, line 5, needs to be updated as necessary. The Office rejects claims 1, 3, 4, 6-8, 10, 11, 40, 41, and 44-61 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1, 3, 4, 6-8, 10, 11, 40, and 41 remain rejected and claims 44-61 are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 1, 3, 4, 6-8, 10, 11, 40, and 41 remain rejected and claims 44-61 are newly rejected under 35 U.S.C. § 102 (e) as allegedly anticipated by U.S. Patent 5,830,755 (the '755 patent). Claims 1, 3, 6-8, 11, 40, 41, 45-47, 50, 52, 56, 58, and 61 are rejected under § 102 (e) as allegedly anticipated by U.S. Patent 6,407,221 (the '221 patent). Claims 1, 3, 6-8, 11, 4-, 41, 45-47, 50, 51, 56, 58, and 61 are rejected under § 102 (e) as allegedly anticipated by U.S. Patent 5,359,046 (the '046 patent). Reconsideration of these allegations and rejections is hereby requested.

The Amendment to the Claims

Claims 62-70 have been cancelled without prejudice. Applicants reserve the right to pursue any cancelled subject matter in a continuation, continuation-in-part, divisional, or

other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter.

Claim 1 has been amended to recite the limitations of claims 3 and 6. Specifically, claim 1 recites "T lymphocyte" and "a recombinant chimeric receptor or a recombinant T-cell receptor." Claims 3 and 6 have been cancelled in view of these amendments. Claim 40 also has been amended to recite "T lymphocyte" and "a recombinant chimeric receptor." Claims 45 and 52 have been amended in view of the amendments made to claims 1 and 40, respectively. Claim 10 also has been amended to recite "recombinant chimeric receptor." Claims 1, 11, 40, and 41 have been amended to recite "which cell is allogeneic to the [T] lymphocyte." Claim 40 also has been amended to recite "and" before "a pharmaceutically acceptable carrier." Claims 46, 50, 56, and 58 have been amended to recite "or a B cell," which recitation is supported in the specification at, for example, page 35, paragraph 83. Claim 41 has been amended to delete the term "antigen," such that it now reads "dual specificity," which is supported by the specification at, for example, page 11, paragraph 42. Claim 71 has been added and is supported by the specification at, for instance, page 17, paragraph 53. No new matter has been added by way of these amendments.

Discussion of the Specification

The Office states that the status of the '263 application, which is cited on page 17, line 5, of the instant specification needs to be updated as necessary. According to the U.S. Patent and Trademark website, however, the status of this application has not changed. The application is still on appeal. Therefore, at this time, the status of the '263 application is correctly recited in the instant specification.

Discussion of the Rejection under 35 U.S.C. § 112, first paragraph

The Office rejects claims 1, 3, 4, 6-8, 10, 11, 40, 41, and 44-61 under Section 112, first paragraph, as allegedly lacking written description. This rejection is respectfully traversed for the reasons set forth below.

Specifically, the Office contends that the scope of the lymphocyte having a second receptor that recognizes *any* cell, which is allogeneic to the lymphocyte, is new matter. However, the use of cells that are allogeneic to the lymphocyte is amply described in the specification. For instance, page 11, lines 1-12, teach that the antigen to which the T-cell receptor reacts can be a strong antigen, including an alloantigen, such as an allogeneic cell. Also, examples of such allogeneic cells are found throughout the specification (see, for

instance, Examples 3-9, and 11. In this regard, the specification does, in fact, provide support for the T-cell receptor recognizing any allogeneic cell.

The Office further contends that the lymphocyte having two receptors comprising (1) an Mov-γ receptor, and (2) an endogenous receptor that reacts with splenocyte, dendritic cell, or peripheral blood cell that is allogeneic to the lymphocyte is new matter. However, such lymphocytes are described in the specification at, for example, page 29, paragraph 77 through page 37, paragraph 85, and page 39, paragraph 87 through page 43, paragraph 107. Specifically, the lymphocyte having two receptors comprising (1) an Mov-γ receptor, and (2) an endogenous receptor that reacts with an allogeneic splenocyte is supported by the specification at, for instance, page 30, paragraph 79. The lymphocyte having two receptors comprising (1) an Mov-γ receptor, and (2) an endogenous receptor that reacts with an allogeneic dendritic cell is supported by the specification at, for instance, page 35, paragraph 83. Also, the lymphocyte having two receptors comprising (1) an Mov-γ receptor, and (2) an endogenous receptor that reacts with an allogeneic peripheral blood cell is supported by the specification at, for example, Examples 7-9.

In view of the foregoing, use of a cell, which is allogeneic to the lymphocyte, is adequately described in the specification of the instant application.

The Office further contends that the phrase "dual antigen specificity" found in claim 41 is new matter. The claimed concept is fully disclosed in the specification as filed. Nonetheless, claim 41 has been amended to delete the term "antigen" thereby obviating the rejection. Applicants note that the specification amply supports the term "dual specificity" at, for example, page 11, paragraph 42.

The Office contends that the "chimeric receptor reactive with a tumor antigen" lacks written description. The Office alleges that adequate written description of a chimeric receptor requires a description of the nucleic acid sequence encoding the chimeric receptor, since the chimeric receptor is made by genetic modification. The Office further alleges that the only chimeric receptor that recognizes a tumor antigen taught in the specification is the Mov-γ receptor. Applicants respectfully traverse.

The instant application is replete with descriptions of chimeric receptors that are reactive with a tumor antigen (see, for example, paragraphs 43-46 and 48-52). For instance, the specification teaches a chimeric receptor comprising a single chain variable region from a monoclonal antibody joined to the Fc receptor chain capable of mediating T-cell receptor signal transduction (page 12, lines 4-7) and a chimeric receptor comprising a variable region joined to the cytoplasmic region of CD28 (page 12, lines 8-11). The specification also teaches a chimeric receptor comprising the alpha, beta, or gamma chain of the IL-2 receptor,

the gamma or alpha subunit of the FcγRIII receptor, the FcεRI, or the alpha or beta chain of the T cell receptor.

The Office alleges that claiming a lymphocyte having a chimeric receptor that recognizes a tumor antigen without teaching the nucleic acid sequence encoding the fragments that are essential to make the chimeric receptor is not in compliance with the written description requirement (page 7 of the Office Action). However, according to the Office's Guidelines for Written Description Requirement, published in the Federal Register, Volume 66, No. 4, page 1101, Response to Comment 9 (January 5, 2001) (copy attached hereto), there is no basis for a *per se* rule requiring disclosure of complete DNA sequences when claiming DNA sequences, let alone when claiming cells that require DNA sequences for the production thereof. In the present case, such description is not required because the specification amply describes the claimed invention without the need to provide any particular DNA sequences. Therefore, the nucleotide sequences encoding the chimeric receptors are not required.

The Office appears to rely solely on the actual reduction to practice of the invention for written description support. However, Applicants respectfully point out that possession of the invention can be demonstrated by a number of ways of which examples showing actual reduction to practice is only one. Manual of Patent Examining Procedure (MPEP) § 2163, II(A)(3) "Possession may be shown in many ways. ... What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. ... If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing even if ever nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." In the present application, the skilled artisan would immediately understand that applicants had possession of the claimed chimeric receptor without the need to refer to a nucleotide sequence. In fact, whereas the skilled artisan could detect that any particular chimeric receptor is chimeric by detailed analysis of the nucleotide sequence, it would be far simpler and more useful to the skilled artisan to simply refer to an embodiment of the claimed invention as including a chimeric receptor."

In view of the foregoing, claims 1, 3, 4, 6-8, 10, 11, 40, 41, and 44-61 are adequately described in the specification of the instant application. Therefore, Applicants request the withdrawal of the rejection of these claims under Section 112, first paragraph.

Discussion of the Rejection under 35 U.S.C. § 112, second paragraph

The Office maintains the rejection of claims 1, 3, 4, 6-8, 10, 11, 40, and 41 and newly rejects claims 44-61 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. This rejection is traversed for the reasons set forth below.

The Office specifically alleges that claim 1 is unclear, since the "chimeric receptor or a T-cell receptor, either of which is reactive with a tumor antigen" can be the "endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte." The Office accordingly concludes that it is unclear as to whether the claimed lymphocyte has one or two receptors. Claim 1 clearly requires two receptors, which is made clear by the conjunction "and." Moreover, when read in light of the specification, it is clear that claim 1 is directed to a lymphocyte having two receptors: one receptor that has reactivity to allogeneic cells, which causes the lymphocyte to become activated and proliferate when exposed to the allogeneic cells, and another receptor that has reactivity to a tumor antigen, which targets cells to tumor-antigen expressing cells (i.e., tumor cells) and causes the lymphocytes to direct their immune response on the tumor cells (see, for instance, page 17, paragraph 53). The former receptor is the endogenous T-cell receptor, which naturally occurs on the surface of a T cell, while the latter receptor is a chimeric receptor or a T-cell receptor that has been made by recombinant means, i.e., that has been genetically engineered.

The term "endogenous" may be at the heart of the Office's allegation. This term is understood in the art to refer to a molecule that is native to a cell, such that the expression of the molecule naturally occurs within the cell and occurs without genetic engineering. One of ordinary skill in the art further understands that a chimeric receptor is never endogenous and is always recombinant, i.e., genetically engineered, since a chimeric receptor is composed of parts of at least two different naturally occurring receptors.

However, in order to advance prosecution and not in acquiescence of the rejection, claim 1 has been amended to recite the limitations of claims 3 and 6, such that claim 1 now recites "T lymphocyte" and "a recombinant chimeric receptor or a recombinant T-cell receptor." Claim 40 also has been amended in similar manner. These amendments make it clear that there are two receptors on the lymphocyte: one that is recombinant and one that is endogenous to the T lymphocyte.

The Office alleges that the phrase "an endogenous T-cell receptor reactive with a cell which is allogeneic to the lymphocyte," which is found in claims 1, 11, and 40, is indefinite. The Office contends that it is not clear as to whether the phrase "which is allogeneic to the lymphocyte" pertains to the cell or the T-cell receptor. However, since the phrase immediately follows the word "cell," it is clear that the phrase describes the cell and not the

T-cell receptor. However, in order to advance prosecution and not in acquiescence of the rejection, claims 1, 11, 40, and 41 have been amended to recite "which cell is allogeneic to the [T] lymphocyte."

The Office further alleges that the term "Mov-γ" is unclear. The Office, in specific, argues that it is unclear as to whether the term is generic to any chimeric receptor. Applicants traverse.

The term "Mov-γ" is clear, such that one of ordinary skill in the art can determine the metes and bounds of the claims. Hwu et al., *J. Exp. Med.* 178: 361-366 (1993), which was incorporated by reference into the application as filed, clearly discloses that Mov-γ was a chimeric receptor constructed using an scFv from MOv18, a monoclonal antibody that is relatively specific for human ovarian carcinoma. Hwu et al. further teaches that the MOv18 antibody is a specific antibody and that it recognizes the 38-kD folate binding protein, which is a surface antigen present on most ovarian carcinomas. The MOv18 antibody is a specific antibody encoded by a genomic nucleotide sequence (see "Construction of Chimeric Genes" of Hwu et al. on page 362). In view of the foregoing, one of ordinary skill in the art understands that the Mov-γ chimeric receptor is not generic to any chimeric receptor that is relatively specific for human ovarian carcinoma. Thus, claims 10, 51, 53, and 57 cannot possibly be "generic to any chimeric receptor having a variable region of a monoclonal antibody and a T-cell receptor γ chain."

Furthermore, the Mov-γ is not limited to "a chimeric receptor having a variable region of a monoclonal antibody and a T-cell receptor γ chain that is specific to ovarian tumor antigen. The γ chain of the Mov-γ chimeric receptor is not the γ chain of a T-cell receptor. Rather, it is the γ subunit that is common to the immunoglobulin (Ig) G and IgE Fc receptors (see, abstract of Hwu et al.). As the purpose of the γ subunit of the Fc receptors is to transmit the signal across the membrane of the lymphocyte once antigen has bound to the chimeric receptor, and since the Fc receptor does not itself bind to the antigen, the γ chain of the Mov-γ chimeric receptor is not specific to any antigen, let alone an ovarian tumor antigen.

The Office also alleges that it is unclear as to whether Mov-γ is an ovarian tumor antigen. However, as discussed above, it is clear that Mov-γ is a chimeric receptor comprising the scFv of the MOv18 antibody and the γ subunit of the IgG and IgE receptors. Therefore, the Mov-γ is not an ovarian tumor antigen receptor. Claim 10 clearly defines Mov-γ as a chimeric receptor. The antecedant basis for the chimeric receptor Mov-γ of claim 10, which depends on claim 4, which, in turn, depends on claim 1, is found in claim 1.

Claim 41 is allegedly indefinite for the recitation of the phrase "dual antigen specificity." Although Applicants do not agree that this claim was indefinite, the rejection has been obviated without narrowing the claim by deleting the term "antigen." Applicants note that the phrase "dual specificity lymphocyte," which is also defined on page 11, paragraph 42, is clear. Thus, the rejection as it pertains to this phrase is moot.

In view of the foregoing, the pending claims of the instant application are clear and definite, such that one of ordinary skill in the art can determine the metes and bounds of the claims. Therefore, Applicants request withdrawal of the rejection of the claims under Section 112, second paragraph.

Discussion of the Rejection under 35 U.S.C. § 102 (e)

The Office maintains the rejection of claims 1, 3, 4, 6-8, 10, 11, 40, 41 and newly rejects claims 44-61 under Section 102 (e) as allegedly anticipated by the '755 patent. Claims 1, 3, 6-8, 11, 40, 41, 50, 52, 58, and 61 are rejected under Section 102 (e) as allegedly anticipated by the '221 patent. Claims 1, 3, 6-8, 40, 41, 45-47, 50, 52, 56, 68, and 61 are rejected under Section 102 (e) as allegedly anticipated by the '046 patent. These rejections are traversed for the reasons set forth below.

Specifically, the Office argues that, since the '755 patent teaches that non-transduced tumor infiltrating lymphocytes (TIL) reacted with murine sarcoma cells (24JK) and because 24JK cells are allogeneic to the TIL, the TIL have an "endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte." Accordingly, the Office alleges that the '755 patent anticipates the claims of the instant application.

The TIL of the '775 patent were non-transduced, and therefore, these TIL were not expressing a recombinant chimeric receptor or a recombinant T-cell receptor that is reactive to a tumor antigen. In this regard, the non-transduced TIL disclosed by the '755 patent are different from the dual specificity lymphocytes of the of the claimed invention, which have two receptors: a recombinant receptor and an endogenous receptor.

In an alternative interpretation of the '755 patent, the Office alleges that the Mov-γ receptor expressed on transduced cells of the '755 patent can be construed as the endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte. However, Mov-γ is a *chimeric* receptor, meaning that it is not endogenous to the TIL. In this regard, the Mov-γ expressed by the TIL of the '755 patent cannot be considered as the endogenous receptor reactive with a cell, which is allogeneic to the lymphocyte.

In yet another alternative interpretation of the '755 patent, the Office contends that the Mov-TIL of the '755 patent inherently has a second receptor that is an endogenous T-cell

receptor reactive with a cell, which is allogeneic to the lymphocyte, since TIL have a wide array of T-cell receptors. The Office assumes that the particular T-cell population transduced in the '755 patent must contain T-cells that are reactive with an allogeneic cell, but Applicants can find no support for this position of the Office in the record. There is nothing in the '755 patent to suggest that the transformed cells included all the T-cells that could possibly be produced by the animal from which they were taken. The Examiner is respectfully requested to point to evidence supporting this position or to withdraw this basis of rejection.

Furthermore, the TIL disclosed by the '755 patent were stimulated by an antigen (see col. 36, line 44) and it is this antigen to which the endogenous receptor should react. Since the '755 patent does not teach what that antigen was, the '755 patent does not teach a lymphocyte expressing Mov-γ and an endogenous receptor that reacts to an allogeneic cell. Therefore, the '755 patent does not teach every limitation of the claims.

The Office further argues that the methods of the '755 patent are the same as that of claim 41. However, the '755 patent does not teach the step of contacting lymphocytes with a cell, which is allogeneic to the lymphocytes. In this regard, the '755 patent does not anticipate claim 41.

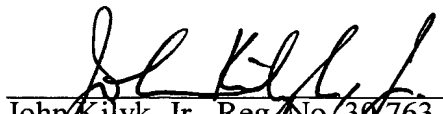
The Office alleges that the '221 and the '046 patents teach lymphocytes transduced with a vector encoding a chimeric receptor that recognizes a tumor antigen and that inherently have a second receptor that is an endogenous T-cell receptor reactive with a cell, which is allogeneic to the lymphocyte. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991) Applicants find no disclosure in the '221 or '046 patents that the transduced cells comprise cells with receptors specific for allogeneic cells. Even if there is a chance that one of the transduced lymphocytes of either the '221 patent or '046 patent has an endogenous T-cell receptor that is reactive to a cell, which is allogeneic to the lymphocyte, it is not an inherent feature of the cells. Accordingly, the claimed invention is not anticipated by the '221 patent or by the '046 patent.

In view of the foregoing arguments, none of the '755, '221, and '046 patents disclose the invention of the pending claims. Therefore, Applicants request that the Office withdraw the rejection under Section 102 (e).

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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